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Original Article

Topiramate as add-on treatment for patients with bipolar mania

KN Roy Chengappa[a,b,c], Dilip Rathore[b], Joseph Levine[a,c], Rebecca Atzert[a,b,c], Lalith Solai[a], Haranath Parepally[a,b], Harry Levin[a], Nicolas Moffa[a], Joyce Delaney[a,b] and Jaspreet S Brar[a]

[a] Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, [b] Special Studies Center, Mayview State Hospital, [c] Stanley Center for the Innovative Treatment of Bipolar Disorder, Pittsburgh, PA 15215-2593, USA

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Objective: Anticonvulsant agents such as carbamazepine and valproate are alternatives to lithium in treating subjects with bipolar disorder. Topiramate (Topamax®), a new antiepileptic agent, is a candidate drug for bipolar disorder. We evaluated topiramate as adjunctive treatment for bipolar patients.

Methods: Eighteen patients with DSM-IV bipolar I disorder [mania (n = 12), hypomania (n = 1), mixed episode (n = 5), and rapid cycling (n = 6)], and two subjects with schizoaffective disorder – bipolar type, resistant to current mood-stabilizer treatment were initiated on topiramate, 25 mg/day, increasing by 25–50 mg every 3–7 days to a target dose between 100 and 300 mg/day, as other medications were held constant for 5 weeks. The Young Mania Rating Scale (Y-MRS), Hamilton Depression Rating Scale (Ham-D), and Clinical Global Impression-Bipolar Version Scale (CGI-BP) were used to rate subjects weekly.

Results: By 5 weeks, 12 (60%) subjects were responders, i.e., 50% reduction in the Y-MRS scores and a CGI of 'much' or 'very much improved'. Three subjects were 'minimally improved', four showed no change, and one was 'minimally worse'. Six subjects had parasthesia, three experienced fatigue, and two had 'word-finding' difficulties; in all cases, side effects were transient. All patients lost weight with a mean of 9.4 lb in 5 weeks, and a significant reduction in body mass index (BMI) occurred too.

Conclusions: Topiramate appears to have efficacy for the manic and mixed phases of bipolar illness. Other preliminary data suggest antidepressant efficacy too. Among obese bipolar subjects, the weight loss potential of topiramate may be beneficial. If controlled trials confirm these initial results, topiramate may be a significant addition to the available treatments for bipolar disorder.

Key words: anticonvulsant – bipolar disorder – depression – mania – psychotic disorders – topiramate – weight loss

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Corresponding author: KN. Roy Chengappa, MD, FRCPC, Associate Professor of Psychiatry, Western Psychiatric Institute and Clinic, Special Studies Center, Mayview State Hospital, Stanley Center for the Innovative Treatment of Bipolar Disorder, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA. Fax: +1 412 624 0493; e-mail: chengappakn@msx.upmc.edu

The use of carbamazepine, an anticonvulsant agent for manic-depressive illness, was first described by Japanese investigators (1, 2). Ballenger and Post (3) conducted the first systematic double-blind trial of carbamazepine for bipolar disorder, and demonstrated the efficacy of this agent for acute mania. Earlier data had suggested that carbamazepine was beneficial for affective symptoms associated with psychomotor epilepsy (4). Several controlled clinical trials have since shown carbamazepine to be beneficial for bipolar illness. Subsequently, Post and Uhde (5) suggested that an animal model of amygdala-kindled seizures could be used to screen candidate anticonvulsant agents as potential treatments for bipolar illness. Since then, another anticonvulsant drug – valproate – was approved as an acute antimanic agent. Newer anticonvulsant drugs, such as gabapentin and lamotrigine, have undergone clinical testing for bipolar illness. One of the second-generation anticonvulsant agents that has received recent attention as a candidate drug for bipolar illness is topiramate (Topamax®)

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(see Appendix A). Topiramate reduced both the seizure score and the after-charge duration in the amygdala-kindled rat (6).

Topiramate is a sulfamate-substituted fructose derivative synthesized in 1980, and a structurally novel antiepileptic agent (7). It was introduced in the USA in 1996 for the adjunctive treatment of adults with partial onset seizure disorder. At the cellular level, topiramate has the following actions: 1) it potentiates the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by inducting a chloride ion flux into the neurons (8); 2) it blocks the state-dependent sodium channel and so limits sustained repetitive firing in hippocampal neurons (9); 3) it antagonizes the ability of kainate to activate the kainate/AMPA subtype of glutamate receptors (with no apparent activity on the NMDA subtype) (10); 4) it also inhibits certain isoenzymes of the carbonic anhydrase enzyme (type II and IV isoenzymes), though this is not believed to be a major component of its antiepileptic activity (7). These actions are thought to underlie its benefits for seizure efficacy. Perhaps some or all of these mechanisms may be involved in the efficacy of this and other anticonvulsant agents for bipolar disorder.

One of the side effects of topiramate may have an unanticipated benefit for overweight subjects with bipolar illness or schizoaffective disorder, i.e., loss of appetite and loss of weight. Clinical data on the use of topiramate for subjects with bipolar and schizoaffective disorder have begun to emerge. So far, these data have mainly been presented at conferences such as the American Psychiatric Association (APA) meeting in Toronto (May and June 1998) and the XXIst Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in Glasgow, UK (July 1998). One study indicated that 5 of 11 (46%) treatment-refractory bipolar I disorder patients responded to topiramate monotherapy treatment. Scores decreased on the Young Mania Rating Scale (Y-MRS, (11)) by 25–50% or greater (12, 13). Yet another study suggested that nearly 62% of a cohort of 58 patients with diagnoses of bipolar I and II disorder, schizoaffective disorder, and other disorders were considered 'moderately' or 'significantly' improved using a global assessment scale (14).

We evaluated topiramate as an add-on adjunctive treatment among patients with DSM-IV-defined (15) bipolar I or schizoaffective disorder – bipolar type.

Methods

Patients with DSM-IV (15) bipolar I disorder (n = 18) and schizoaffective disorder – bipolar type (n = 2) who provided consent were treated openly with topiramate. Diagnosis was ascertained in all cases by the first author by a combination of interviews, discussions with the attending psychiatrist if not directly under the care of the primary author, review of all available records, and in some subjects, discussion with family members. These patients had failed to respond to combination treatments with mood-stabilizing agents and/or antipsychotic agents, and were continuing to experience either manic or mixed symptoms (see Results below, and Tables 1 and 2).

All subjects and involved family members were advised of the risks and benefits of topiramate, based on the published literature for seizure disorders, as well as the emerging data on the use of topiramate for bipolar and schizoaffective disorder. They were also advised that this use of topiramate would be 'off-label' for bipolar or schizoaffective disorder. Alternative therapies were discussed with patients as well.

Relevant demographics, diagnoses, and other clinical details were collected at the first interview. The following psychiatric ratings were done weekly for 5 weeks: Y-MRS, (11), Clinical Global Impression-Bipolar Version Scale (CGI-BP) (severity and

Table 1. Patient characteristics (n = 20)

Age, mean ± SD (range)	43 ± 14 (21–67) years	
Gender	8 males, 12 females	
Ethnicity	18 Caucasian, 2 African-American	
Diagnosis (DSM-IV)	n	%
Bipolar I disorder	18	
Schizoaffective disorder – bipolar type	2	
Mood state at entry		
Manic with psychoses	11	55
Manic without psychoses	3	15
Mixed	5	25
Hypomania	1	5
Secondary features		
Rapid cycling	6	30
Borderline personality	3	15
Partial complex seizure disorder	1	5
Recent substance and alcohol abuse or dependence	10	50
Age at first hospitalization		
Mean ± SD (range) years	24 ± 5 (16–34)	
Number of psychiatric hospitalizations		
Mean ± SD (range)	10.5 ± 7 (2–30)	
Duration of current episode		
Mean ± SD (range) weeks	9.4 ± 5 (3–22)	
Duration of abstinence from drugs and/or alcohol		
Mean ± SD (range) weeks	12.8 ± 4 (8–29)	

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Table 2. Pharmacological treatment during the current episode

Name of drug	n	Dose mg/day (mean ± SD)	Levels	Duration of treatment (weeks) (mean ± SD)	Response
Lithium	6	1140 ± 390	0.8–1.3 mEq/l	9.1 ± 4	Partial = 2 Poor = 4
Valproate*	11	1955 ± 550	60–110 mg/l	8.7 ± 4	Partial = 4 Poor = 7
Carbamazepine*	4	900 ± 622	6–11 mg/l	8.9 ± 4	Partial = 1 Poor = 3
Gabapentin*	5	1760 ± 434		7.3 ± 3	Partial = 2 Poor = 3
Antipsychotic					
First generation	4			8.4 ± 4	
Second generation**	10			8.2 ± 4	

*Three subjects received a combination of lithium and valproate, one subject received carbamazepine and lithium, two subjects received valproate and carbamazepine, and all subjects receiving gabapentin were also receiving either valproate or carbanazepine.
**Clozapine n = 2, risperidone n = 2, olanzapine n = 4, and quetiapine n = 2.

improvement, CGI-S and CGI-I, respectively) (16), and the Hamilton Depression Rating Scale (Ham-D, 21 items) (17). After 5 weeks, ratings were done less frequently. As this was an add-on study, psychotropic drugs remained unchanged for 5 weeks. Also, spontaneously expressed and elicited side effects were recorded. Levels of mood-stabilizers (lithium, valproate, and carbamazepine) were done per the practice of the treating psychiatrist rather than specifically for purposes of the study. Patients were weighed wearing light clothing prior to initiation of the study and at each subsequent visit using the same weighing machine and approximately at the same time of day each week. Patients' height was recorded too. Body mass index (BMI) was calculated based on the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults released by the National Heart, Lung, and Blood Institute in June 1998 (18). The nonmetric conversion formula, BMI = [weight (lb) ÷ (height)^2] × 704.5.

Dose, dosing, and titration

In the absence of data on the daily dose requirements of topiramate for bipolar illness, we targeted a lower dose of 100–300 mg/day based on data presented by Marcotte and Gullick (14). Dosing and titration were done on an individualized basis and, in general, titration was done slowly. All subjects were started at a dose of 25 mg/day, and increments of 25–50 mg were planned every 3–7 days, unless intolerance dictated a slower titration. Three subjects who were able to tolerate topiramate were titrated faster. Subjects did not have psychotropic medications altered for at least 1 week prior to receiving topiramate. Other psychotropic medications were not altered for the first 5 weeks after topiramate was initiated.

Statistics

As this is an open study, main efficacy variables as well as weight and BMI were evaluated using the Wilcoxon signed-ranks test, using a pre–post period of time. The Pearson correlation was used to test statistical differences in the initial and 5-week weights among all subjects.

Results

Patient characteristics

Seventeen subjects were inpatients and three were outpatients (see Tables 1 and 2 for demographics, illness characteristics, and past treatment history). All subjects had failed adequate trials (range: 7–9 weeks) of one or two mood-stabilizing agents used either singly or in combination during the most recent episode, and 14 subjects were also receiving an antipsychotic agent and an anxiolytic agent for nearly the same period of time (Table 3). Eleven subjects (including the two schizoaffective subjects) had psychotic symptoms associated with mania, of whom eight subjects had mood-congruent delusions. Ten subjects had comorbid alcohol or substance dependence or abuse diagnoses by DSM-IV (15) within the past 6 months. However, 17 of the 20 subjects had been hospitalized in a community hospital prior to being transferred to the state psychiatric hospital, and subsequently they had been abstinent from alcohol or substance use for an average of nearly 13 weeks, and remained severely

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Table 3. Previous mood-stabilizer treatment

Name of drug	n	Dose mg/day mean ± SD	Levels	Duration of treatment (weeks) mean ± SD	Response[a]	Side effects
Lithium	20	1448 ± 447	0.7–1.3 mEq/l	40.5 ± ≥6	Good = 10 Minimal–modest = 4 Poor = 6	Weight gain = 12 Hypothyroidism = 14 Tremors = 8 Polyuria and Polydipsia = 9
Valproate	20	1895 ± 597	55–105 mg/l	27 ± 12	Good = 9 Minimal–modest = 4 Poor = 7	Weight gain = 9 Tremors = 6 Hair thinning = 6 Abnormal LFT[b] = 3
Carbamazepine	11	664 ± 169	5–11 mg/l	17.5 ± 17	Good = 5 Minimal–modest = 3 Poor = 3	Rash = 3 Abnormal LFT[b] = 3 Drug interactions = 3
Gabapentin*	8	1875 ± 337		9.6 ± 4	Good = 3 Minimal–modest = 1 Poor = 4	
Lamotrigine*	3	N/A		8	Good = 1 Poor = 2	Rash = 1

N/A, not available.
*Gabapentin and lamotrigine were administered only in combination treatment, either with valproate or lithium.
[a] Mainly reviewed for previous manic, hypomanic, or mixed episodes and not for depression. Due to nonavailability of more complete chart data, it is not possible to conclude on effectiveness for prophylaxis.
[b] Liver function tests.

manic prior to receiving topiramate. One subject with schizoaffective disorder – bipolar type received topiramate for 4 weeks, and was discharged against medical advice. In the case of the three outpatients, breakthrough mania occurred in two individuals, and one had emergent hypomania. Available data suggest that these three outpatients were adherent to their prior treatments, and blood levels of the thymoleptic agents prior to topiramate initiation were within the therapeutic range.

Dose and duration of treatment

The mean dose of topiramate was 42.5 mg/day in the first week (range: 25–100 mg); 87.5 mg in the second week (range: 50–200), 141.3 mg in the third week (range: 0–225 mg), 192.5 mg in the fourth week (range: 0–300 mg), and 210.5 mg in the fifth week (range: 50–300 mg). One patient was discontinued from topiramate treatment during weeks 3 and 4 due to confusion, and this accounts for the zero in the range of topiramate dosing noted above. He subsequently responded to a slower titration. The average duration of topiramate treatment was 142 days (range: 29–293 days).

Efficacy measures and responders

Based on a priori criteria, 'responders' to topiramate were those who achieved 50% or greater reduction in the Y-MRS score (from baseline) during a 5-week period and a CGI-I score of 2 or less (i.e., 'much improved' or 'very much improved'). Twelve patients (60%) were 'responders' to topiramate. This number included one subject who had to discontinue topiramate for 2 weeks due to 'acute mental status' changes, and was then re-challenged with a slower titration, and achieved a good clinical outcome, see Table 4. The time taken to reach this response criterion ranged from 2 to 4 weeks. The responders appeared to show a steady decline in the weekly Y-MRS and CGI-S scores, see Table 5.

Table 4. Treatment response

	n	%
Responders*	12	60
Minimal improvement	3	15
No response	4	20
Minimal worsening	1	5
Subcategories		
Rapid cycling (n = 6)	4	67
Borderline personality (n = 3)	1	33
Alcohol and substance use or dependence (n = 10)	6	60
Mixed mood state (n = 5)	3	60
Manic psychoses (n = 11)	6	55
Schizoaffective disorder – bipolar type (n = 2)	1	50

*50% or greater reduction in Young Mania Rating Scale *and* Clinical Global Impression-Bipolar Version Scale of 'much' or 'very much' improved.

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Table 5. Response to topiramate treatment: change in assessment scores*

		Mean score ± SD
Young Mania Rating Scale	Baseline	29.7 ± 10
	3 weeks	18.4 ± 10
	5 weeks	11.6 ± 9
Hamilton Depression Rating Scale (21 items)	Baseline	13 ± 4
	3 weeks	9.5 ± 4
	5 weeks	8.5 ± 4
Clinical Global Impression-Bipolar Version Scale		
Severity	Baseline	5 ± 1
	3 weeks	4 ± 1
	5 weeks	2.6 ± 1
Improvement	3 weeks	3.4 ± 1
	5 weeks	2.5 ± 1

*The Wilcoxon signed-ranks test and the ANOVA test showed statistical significance from baseline to either 3 or 5 weeks, results are available upon request.

Three subjects improved on the Y-MRS scores from 25 to 50% in the 5-week time period, and the CGI-I scale was rated as 'minimally improved'. Four subjects showed no response and one subject was rated as 'minimally worse' on the CGI rating. None of the subjects showed a worsening of the Ham-D scores, and among those subjects with a 'mixed' presentation, the Ham-D scores improved in the same time period as the Y-MRS scores. Among those responding subjects with manic psychoses at presentation, the specific item in the Y-MRS related to content of thinking that includes paranoid and grandiose ideas and ideas of reference or delusions or hallucinations improved over the same time course as the rest of the items. No separate rating scale for psychoses was used in this study.

Response characteristics of the subgroups of subjects are reported in Table 4. An additional point merits emphasis. Even though impulsivity and hostility were not measured separately, in at least six subjects (among the 'responders' and 'minimal responders'), there were clinically important and readily apparent reductions in aggressive behavior. For instance, a decrease in seclusion and restraint, near abolition of self-mutilation in two subjects with the added diagnosis of borderline personality disorder, and the decreased use of emergency medications for agitation. These improvements were noted in the first 2–4 weeks of topiramate treatment and were sustained. Six of the eleven subjects who had psychotic manias responded to topiramate; five of these responding subjects had mood-congruent psychotic symptoms.

Adverse effects

Adverse events were seen in the first 3–4 weeks, and resolved either without treatment or by dosage reduction. These side effects included mild parasthesia of the hands (n = 5), jaws and upper lips (n = 1), anorexia (decreased appetite) (n = 5), fatigue (n = 3), sedation (n = 2), slowed thinking (n = 3), word-finding difficulty (n = 2), tremor (n = 1), and nausea (n = 1). In one subject, 'acute mental status' changes were noted. The titration was faster than other subjects in his case, and he was dosed to 200 mg by day 10 as an outpatient. It must be noted that he was receiving clozapine (250 mg) and valproate (2000 mg) concomitantly. He was described as 'confused' – disoriented to time and place, had word finding difficulty, and was excessively somnolent over a period of 2 days. He was admitted to a local hospital, and an EEG, CT scan, and MRI of the brain were within normal limits. Topiramate was discontinued and he was discharged within a day as his acute mental status changes had returned to normal. However, his manic and psychotic symptoms worsened. Two weeks later, following discussions with him, his family, and the staff members where he resided, there was consensus that he had shown some early improvement with topiramate prior to the 'confusional' state. So, a re-challenge with topiramate was undertaken with a slower titration. He responded positively the second time, and without problems. One subject had an itching maculopapular type of rash over the extensor surfaces of both arms and both knees, which appeared during weeks 3 and 4, and resolved with the use of and emollient cream and oral diphenhydramine treatment for 7 days, and treatment with topiramate continued uninterrupted. Importantly, all these adverse effects occurred singly or in combination in nine subjects, and interestingly no adverse effects were elicited or reported by 11 subjects. No particular clinical characteristics distinguished either group, though the group without adverse effects appeared to have fewer concomitant medications overall. Yet another point of note is that among the five subjects with noninsulin-dependent diabetes mellitus, three subjects achieved good glycemic control, without any additional changes in the diabetic regimen. These subjects did lose weight (see section on weight below).

Follow-up

Details of the follow-up of subjects ranging from 29 days to 10 months are provided in Table 7. Two subjects with a rapid cycling course experienced a

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manic episode and hypomanic episode 7 and 6 months later, respectively, and responded to an increment in the topiramate dosage. Four of the discharged individuals achieved an eventual reduction in polypharmacy. Lorazepam or clonazepam was discontinued in four subjects, and anti-psychotic agents were discontinued in three subjects. Those subjects who had a reduction in polypharmacy experienced a further reduction of side effects.

Weight and BMI

The effects of topiramate on weight were evaluated weekly for the first 5 weeks and less frequently thereafter. Prior to topiramate treatment, the average weight for the group was 212.3 ($\pm$ 54) lb, and the BMI was 34.4 (i.e., in the 'obese' category), see Table 6. There was a significant weight loss for the group; an average of 9.4 lb over 5 weeks, with an average weight loss of 1.5–2 lb/week. All patients lost weight, although three subjects gained 2–5 lb for the first 2 weeks, and then eventually lost weight. Similarly, significant decreases in the BMI were noted in this study. At baseline, two subjects had a normal BMI between 18.5 and 25 (18). Three subjects were in the 'overweight' BMI category of > 25 but < 30, and 15 subjects were in the 'obese' BMI category of ≥ 30, of whom three subjects were in the 'extremely obese' BMI category of ≥ 40. None of the subjects moved into the 'underweight' BMI category of < 18.5 during the 5 weeks of topiramate treatment or the subsequent follow-up period. Interestingly, those with a BMI ≥ 30 (i.e., obese) lost more weight, nearly 10.2 lb, compared to those with a BMI < 30 who lost 7 lb in 5 weeks (see Fig. 1). Overall, subjects who were heavier to begin with lost more weight eventually (Pearson correlation = 0. 61, p = 0.007). In the follow-up of individuals (up to 10 months in some individuals), there has been a further reduction in weight, more evident among the 'obese' BMI category. Serum lipids were not measured.

Mood-stabilizer levels

Mood-stabilizer levels (lithium, valproate, and carbamazepine) were measured once for all subjects, and twice for eight subjects during the 5 weeks of topiramate treatment. No significant alterations were noted from the previous therapeutic ranges for lithium or valproate or carbamazepine. However, there was no systematic collection of the serum levels to comment more definitively on this issue. Topiramate levels were not evaluated and are not recommended for routine monitoring in subjects with epilepsy.

Discussion

These data suggest that topiramate may be a useful adjunctive treatment in some patients with bipolar I disorder and schizoaffective disorder – bipolar type who have otherwise not responded to combination treatment strategies. All subjects in this study received topiramate as an add-on treatment to their ongoing treatment regimen. The majority of subjects in this series were inpatients who had failed adequate trials of combinations of mood stabilizers and antipsychotic and anxiolytic agents for the present episode in the weeks prior to topiramate initiation.

Table 6. Weight and body mass index (BMI) change with topiramate treatment

Time of evaluation	n	Baseline weight mean $\pm$ SD (range) lb	Weight reduction from baseline mean $\pm$ SD (range)	Baseline BMI mean $\pm$ SD (range)	BMI reduction from baseline, mean $\pm$ SD (range)
Baseline	20	212.3 $\pm$ 54 (139–348)		34.4 $\pm$ 7.55 (21 to 52.4)	
1 week	20		−1.8 $\pm$ 2 (−6 to +5)*		−0.30 $\pm$ 0.4*** (−0.89 to +0.6)
3 weeks	19[b]		−5.7 $\pm$ 3 (−15 to −1)**		−0.91 $\pm$ 0.4** (−1.88 to −0.16)
5 weeks	20		−9.4 $\pm$ 5 (−23 to −3)**		−1.49 $\pm$ 0.7** (−2.88 to −0.49)
Follow-up visit[a]	19[c]		−13.4 $\pm$ 12 (−46 to −3)**		−2.09 $\pm$ 1.6** (−5.76 to −0.49)

[a] In some subjects the duration of follow-up was 10 months.
[b] One subject dropped out at 4 weeks.
[c] One subject was lost to follow-up at 4 weeks.
*p = 0.006 (compared to baseline).
**p = 0.001 (compared to baseline).
***p = 0.002 (compared to baseline).

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Table 7. Follow-up treatment with topiramate of bipolar patients[a]

Age/gender	Diagnosis	Duration of follow-up (months)	Outcome	Patients who relapsed	Comments
54/F	BPI, manic psychoses, RC	7	Discharged to community residence	Manic episode after 7 months	Definite improvement in cycling with greater inter-episode 'well' periods. Significant decrease in hospitalizations.
64/M	BPI, manic psychoses	10	Remains in hospital		Taper and discontinuation of gabapentin and anxiolytic successful.
53/F	BPI, manic psychoses	10	Discharged home		Combination treatment of valproate tapered and discontinued, olanzapine continues.
38/F	SA–bipolar type	7	Discharged to community residence		Significant reduction in resource utilization and self destructive behavior in community.
21/F	BPI, mixed	7	No change		Topiramate discontinued after 6 months. Remains hospitalized.
52/M	BPI, manic psychoses, RC	10	Good	Hypomanic after 6 months	Significant improvement in cycling. Significant weight loss. Good diabetes control.
36/M	BPI, manic, RC	10	Good	Cycling continues	Good diabetes control. No further complex partial seizures. Some weight gain since the addition of olanzapine.
25/F	SA–bipolar type	2	Discharged against medical advice	Relapsed into severe mania	Discontinued medicines upon discharge. One month later rehospitalized.
24/M	BPI, mixed	10	Awaiting out of state discharge		Much improved, but no further aggression. Significant weight loss.
55/M	BPI, manic psychoses	8	No improvement		Topiramate tapered and discontinued. Improved partially on reintroduction of lithium and anxiolytic.
67/F	BPI, manic psychoses	8	No improvement		Topiramate being tapered, partial improvement on risperidone and valproate. Good diabetes control.
42/M	BPI, manic psychoses	6	Minimally worse		Significant weight loss. Good diabetes control.
28/F	BPI, manic	7	Good		Significantly improved, decrease resource utilization. Significant weight loss on topiramate monotherapy.
46/F	BPI, mixed	4	Discharged to community residence	Mild hypomanic episode 4 months later	Significant improvement. Minimal weight loss.
61/F	BPI, manic, RC	8	No change		Weight loss prominent. Maintenance ECT.
45/F	BPI, manic psychoses	4	Discharged to community residence		Remarkable and notable improvement on topiramate and risperidone.
45/F	BPI, mixed, RC	3	Discharged home		Significant improvement in cycling and impulsive behavior. Reduction in concomitant medications achieved.
41/F	BPI, manic psychoses	3	Near discharge		Notable improvement on topiramate and risperidone. Reduction in valproate and anxiolytic. Lithium continued.
26/M	BPI, manic psychoses	2	Good response		Notable improvement with topiramate and risperidone.
23/M	BPI, mixed	2	Partial response so far		Partial response to topiramate and quetiapine.

[a] BPI, bipolar I disorder; RC, rapid cycling; SA – bipolar type, schizoaffective disorder – bipolar type.

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Diagnosis, mood state at entry, and efficacy

This case-series supports the data that are emerging on the use of topiramate for bipolar mania. Calabrese et al. (13) reported that 5 of 11 (46%) treatment-refractory hospitalized bipolar I disorder patients benefited from topiramate monotherapy based on Y-MRS decrease by 25–50% or greater. Marcotte and Gullick (14) noted 62% of a cohort of 58 diagnostically heterogeneous outpatients (19 were inpatients) were considered 'moderately' or 'markedly' improved using an investigator global assessment with topiramate added on to previous treatment. McElroy et al. (19) noted 10 of 20 (50%) subjects who were initially manic were rated as 'much' or 'very much improved' on the CGI-BP. However, the average Y-MRS of 10.6 prior to receiving topiramate in a group that included 'manic', 'hypomanic', 'mixed', and 'rapid cycling' suggests subjects entering the McElroy study were mainly outpatients who had relatively mild symptoms (19).

Preliminary data suggest topiramate may have antidepressant efficacy in bipolar illness. A Canadian study reported that 11 of 20 (55%) bipolar I or II depressed patients who completed an adequate trial responded positively when topiramate was added openly to ongoing mood stabilizer and other treatments (20). McElroy et al. (19) found that four of eight (50%) bipolar depressed subjects were rated as 'much' or 'very much improved' using the CGI-BP.

Marcotte and Gullick (14) reported that 23 of 44 (52%) rapid-cycling subjects responded. Eleven subjects (33%) of the cohort reported by McElroy et al. (19) had rapid cycling. However, the data on their response are not separately available. In our study, four of the six rapid-cycling subjects met the responder criteria in the acute phase, although, as noted in the follow-up phase, two subjects relapsed into mania and hypomania.

An open trial such as the present study is limited by the selection of an heterogeneous subject population, the lack of active or placebo comparison groups, and the potential bias of the raters and subjects.

Data from larger double-blind controlled trials using random assignment, placebo, and active comparator controls (either in monotherapy or adjunctive treatment) are likely to provide better estimates of the efficacy of topiramate in both short- and long-term treatment. It is also possible that these rates will be different in either responsive or nonresponsive patients or among those with bipolar I or II disorder or schizoaffective disorder – bipolar type. Additional information of the potential benefits of topiramate for patients who evidence a rapid-cycling course will probably accrue from such trials as well. Finally, data on potential prophylactic efficacy await systematic trials.

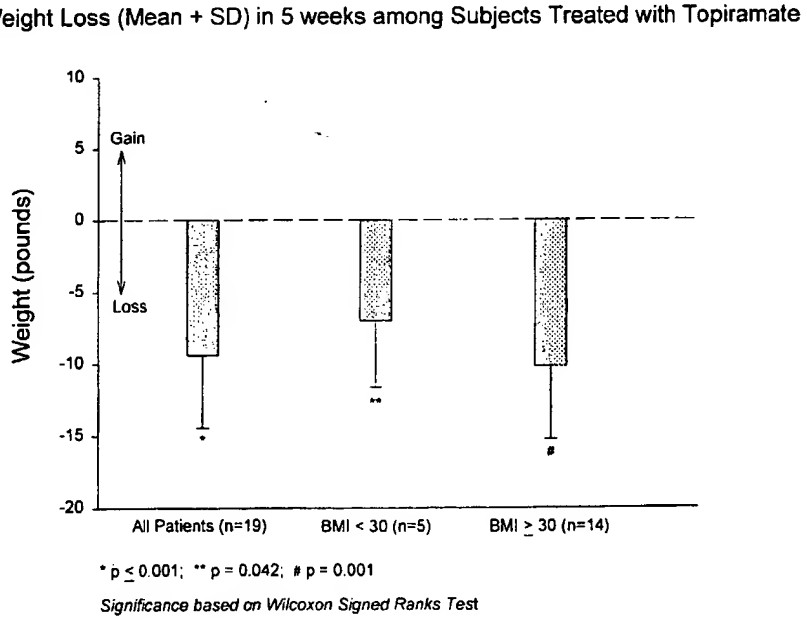

Fig. 1. Weight loss (mean ± SD) in 5 weeks among subjects treated with topiramate.

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Dose, dosing, titration, and blood levels

Outpatient studies, using an add-on strategy with topiramate and targeting either hypomania, mania, mixed, or depressed episodes, appear to target between 100 and 300 mg/day, with an average of 200 mg/day (14, 19, 20). Though the present study was mainly inpatient, we too targeted the same dose. The titration in the studies noted earlier was generally slow, starting at 25–50 mg/day and increasing every 3–7 days by 25–50 mg to the target dose. In contrast, Calabrese et al. (13) titrated much faster (50–150 mg daily) and to a higher target dose (1300 mg), but this was monotherapy and in refractory bipolar I inpatients, and the mean dose was 614 mg/day.

Data from epilepsy clinical trials, where topiramate was added on to other antiepileptic agents, suggest rapid dose escalation and a target dose greater than 400 mg/day lead to more adverse effects and discontinuations (21–26). These data also suggest that subjects with epilepsy who were successfully switched from 2 to 3 drug regimens to topiramate monotherapy had a significant decrease in side effects. So, the data from epilepsy regarding dosage escalation and simplification of complex pharmacological regimens may apply to bipolar disorder as well. However, in many bipolar subjects, attempts to decrease combination therapy may be difficult to achieve in practice. So far, data on topiramate levels and response in bipolar illness are unavailable. There is no recommendation for routine monitoring of topiramate blood levels in epilepsy.

Time to response

Marcotte and Gullick (14) noted some subjects 'improved' with topiramate treatment within 72 h. In the present study, the earliest 50% decrease on the Y-MRS scores was noted by week 2 for four of the responding subjects, and the rest took longer to respond.

Safety and tolerability

The common side effects noted in bipolar patients seem similar to those reported among patients with epilepsy. These appear to be mainly related to the CNS or gastrointestinal systems. Somnolence, fatigue, difficulty with concentration, dizziness, parasthesia, anorexia, weight loss, nausea, and vomiting seem mild to moderate in severity and occur early in treatment. Some side effects appear to be related to rapid dose escalation and higher doses in epilepsy (21–26), and similar patterns seem to be emerging for bipolar illness as well. Also, similar to the data from epilepsy clinical trials, available data among bipolar subjects suggest that those on complex pharmacological treatments are more vulnerable to side effects. So, it is possible that a slower dosage titration, a lower target dose, and simplification of the treatment regimen will help minimize some of the side effects associated with topiramate.

Weight loss and BMI

The mechanism(s) underlying the ability of topiramate to induce weight loss remains to be established. Data from short- and longer-term epilepsy studies suggest weight loss was typically noted in the first 3 months, and continued for up to 15–18 months of treatment (27). Subjects receiving higher rather than lower doses lose more weight and women lose more weight than men (27). Another group noted weight loss of nearly 8 kg in 28 valproate-treated patients with epilepsy who were either switched to topiramate monotherapy or received topiramate concomitantly (28). Weight loss in 12 phenytoin- or carbamazepine-treated subjects with epilepsy who received topiramate was around 3 kg (28).

Data on weight loss and BMI in topiramate-treated bipolar subjects appear to be consistent, too. In the Calabrese et al. study (13), three subjects weighing 100 kg or more lost weight: two subjects lost 2 kg and one subject lost 7 kg in 28 days. In the McElroy et al. study (19), at 1 month, 29 subjects had lost an average of 0.7 kg, at 2 months, 23 remaining subjects had lost 2.4 kg, at 3 months, 18 remaining subjects had lost 2.8 kg, and at 6 months, the remaining 11 subjects had lost 6.9 kg. These data appear to support our findings on weight and BMI in bipolar subjects. Interestingly, we noted that heavier subjects in the obese category seemed to lose more weight, similar to those reported in the epilepsy literature (27).

When questioned regarding their appetite and satiety, a few subjects in our study clearly noted they did not feel the urge to eat certain foods to excess (chocolates, 'junk' foods, etc.) and felt satiated sooner. We did not measure serum lipids, and so do not know if topiramate has any effects on these measures. Future studies evaluating weight may shed more light on this important property of topiramate. Another benefit of topiramate was noted among the diabetic subjects, whose weight loss coincided with improved blood glucose control. It would be clinically prudent to weigh the risks versus the benefits of topiramate treatment in anorexic or seriously underweight subjects.

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Summary

Based on data from preliminary but open studies, systematic investigations using topiramate are now underway for acute manic and mixed episodes associated with bipolar I disorder. These systematic and related data will likely provide more definitive data on dose, dosing and titration, and the target doses of topiramate, and whether it has efficacy for acute and maintenance phases of bipolar illness. Anorexia and weight loss may be a particularly advantageous property of topiramate, especially for the treatment of those bipolar subjects that are overweight or obese. Lithium and valproate are associated with significant weight gain in a subgroup of bipolar subjects. Also, if these agents are combined with certain antipsychotic agents with potential for weight gain, there can be the induction or worsening of associated medical conditions, such as diabetes mellitus or hypertension or sleep apnea, among others. In addition, significant weight gain may lead to nonadherence of treatment by patients, which in turn can have serious and adverse consequences. There are additional preliminary and intriguing data that topiramate may be beneficial for some bipolar subjects with additional diagnoses of substance or alcohol abuse or dependence, borderline personality, and rapid cycling. If these early benefits of topiramate are replicated in controlled trials, then topiramate is likely to be a useful addition to the treatments becoming available for subjects with bipolar and related disorders.

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Appendix A

Pharmacology of topiramate

Topiramate offers certain pharmacological advantages: a) it is rapidly absorbed, and food slows absorption, but the extent of absorption remains the same; b) it is minimally protein-bound (< 20%); c) it is minimally metabolized (20%); d) it is excreted mostly unchanged in the urine; e) the parent compound is responsible for most of the activity, and there are no active metabolites; and f) it has an elimination half-life of 19–23 h with linear pharmacokinetics in the 100–1200 mg dose range (29). These properties permit once or twice daily administration that may encourage compliance among subjects. Twice daily administration may help diminish 'peak' level side effects in vulnerable subjects, although administering the dose at bedtime may help counter this as well. Topiramate also has a low potential for drug–drug interactions, which is especially important when subjects are receiving several pharmacological agents, which is especially common among subjects with bipolar illness. Enzyme-inducing antiepileptic agents decrease topiramate concentrations: phenytoin by 48%, carbamazepine by 40%, and valproic acid by 14% (29). So, the addition or subtraction of carbamazepine or phenytoin may require dosage adjustments of topiramate. However, topiramate appears not to alter steady-state carbamazepine or valproate. Topiramate may decrease lithium levels minimally. Dosage adjustments may be necessary for coadministration with digoxin, as the area under the curve was decreased by 12% (29). Also, the efficacy of oral contraceptive drugs may be reduced by topiramate (29), so appropriate information needs to be given to women in the child-bearing age. Topiramate is classified as a Pregnancy Category C drug (29), and it is excreted in the milk of lactating rats. So, it should be used in pregnant women only after a careful consideration of the risks and benefits. Subjects with renal impairment may need topiramate dosage adjustments, as it is predominantly (80%) cleared through the kidneys. A total of 32 of 2086 (1.5%) patients exposed to topiramate during its development reported the occurrence of kidney stones (30, 28). As in the general population, the incidence of stone formation among topiramate-treated patients was predominantly in men. An explanation for the association of topiramate and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. So, it would be prudent to avoid combining other carbonic anhydrase inhibitors with topiramate. Additional precautions may be needed in subjects with parathyroid disorders or gout, or those subjects using antacids, which may deplete phosphate, or subjects with an excess intake of milk and alkali (31). Also, when the renal stones were analyzed, these were apatite stones (calcium phosphate) (30). It has been suggested that a liberal fluid intake and adequate hydration may help diminish this risk.

Speculation on the mechanism(s) of action of topiramate for bipolar illness

Post and Uhde (5) suggested that an animal model of amygdala-kindled seizures could be used to screen candidate anticonvulsant agents as potential treatments for bipolar illness. This was based on

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their studies of carbamazepine for bipolar illness. Topiramate is effective in reducing both the seizure score and the after-charge duration in the amygdala-kindled rat (6). Decrease of neuronal excitability by inhibiting Na^+ channels is a property shared by valproate, carbamazepine, lamotrigine, and topiramate. This property among anticonvulsant agents may be important for efficacy in both seizure disorders and bipolar disorders. It has been suggested that low plasma GABA is a trait-like marker for bipolar illness (32). Similar to valproate, topiramate augments neuronal responses to GABA (8), and increases cerebral GABA concentrations in healthy individuals within hours (33), which may partially explain its benefits for subjects with bipolar illness. Glutamate is the predominant excitatory neurotransmitter in the brain, and topiramate is an antagonist at the AMPA/kainate type of glutamate receptor (9), and this may be an additional mechanism that is important in mediating bipolar illness. Topiramate also negatively modulates L- and N-type calcium channels and has uncertain effects at T-type channels. The calcium channel-blocking drugs, such as verapamil and nimodipine, have shown mixed results in acute mania, though some patients have responded favorably. Finally, acetazolamide, a carbonic anhydrase inhibitor, has been cited to be useful in bipolar disorders (34, 35). Topiramate inhibits type II and IV isozymes of carbonic anhydrase, and this may be relevant to its benefits for patients with bipolar disorder.

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